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Intrauterine environment and food intake

PART 1

Lower birth weight is associated with alterations in dietary intake in adolescents independent of genetic factors: a twin study

III

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ABSTRACT

BACKGROUND & AIMS

Lower birth weight is associated with an increased risk of cardiovascular and metabolic disease. These associations may, at least in part, be explained by alterations in dietary intake in later life. The aim of this study is to examine whether lower birth weight is associated with alterations in dietary intake in later life, and whether this association is due to intrauterine environmental or genetic factors.

METHODS

In this observational study birth weight and dietary intake were investigated in 78 dizygotic (DZ) and 94 monozygotic (MZ) adolescent same-sex twin subjects. Birth weight was obtained from the mothers. Dietary intake was assessed by two-day dietary records.

RESULTS

In the total group of twins, lower birth weight was associated with higher intake of saturated fat after adjustment for current weight (1.2 per cent of total energy intake (E%) per kg increase in birth weight, $P<0.01$). Intra-pair analysis in all twin pairs demonstrated that twins with the lower birth weight had a 115 kcal higher total energy intake and a 0.7 E% higher saturated fat intake compared to their co-twins with the higher birth weight ($P<0.05$). Intra-pair differences in birth weight were negatively associated with differences in energy intake and differences in intake of saturated fat after adjustment for differences in current weight ($P=0.07$ and $P<0.05$, respectively). Intra-pair differences in birth weight were positively associated with intra-pair differences in intake of dietary fibres ($P<0.05$). These intra-pair differences and associations were similar for DZ and MZ twins (P for difference >0.6).

CONCLUSIONS

Lower birth weight was related with higher intake of energy and saturated fat within twin pairs, and these associations were independent of zygosity, suggesting that the association between birth weight and alterations in dietary intake in later life are explained by intrauterine environmental rather than genetic factors.

INTRODUCTION

In the last twenty years, many epidemiologic studies have shown that lower birth weight, a measure of reduced foetal growth, is associated with increased incidence of hypertension, type 2 diabetes and cardiovascular disease [1-4]. Several studies in singletons suggested that the association between lower birth weight and the increased risk to develop metabolic and cardiovascular disease may, at least in part, be explained by changes in dietary intake [5-8].

The origin of the possible association between birth weight and dietary intake in later life is not completely understood. The leading hypothesis proposes the programming of dietary preferences in reaction to a poor intrauterine environment. Such adaptive programming would be favourable if nutrition remained insufficient after birth. However, if nutrient availability becomes abundant, maladaptive consequences, such as obesity and type 2 diabetes, may occur [9]. This hypothesis is supported by two studies demonstrating that early prenatal exposure to undernutrition during the Dutch famine is associated with higher energy intake and a favour for diets rich in fat in later life [10, 11].

An alternative explanation states that the association between birth weight and dietary intake arises from pleiotropic genetic factors [12, 13]. In other words, the genotype responsible for the intake of an unhealthy diet may itself cause reduced foetal growth in utero. Such a genetic effect cannot be ruled out by the Dutch famine studies since these studies might have been influenced by selection bias. During the Dutch famine, the number of conceptions was about 50% lower than the pre-famine level and perinatal mortality as well as mortality in the first year after birth were higher in those who were born during the famine [14]. Thus, if women with specific dietary intake conceived more often and/or if their children survived more often, a genetic effect on dietary intake would cause these children to eat more or differently in later life.

If genetic factors are responsible, improving the intrauterine environment will not likely influence dietary intake in later life. If the association between birth weight and dietary intake is due to an intrauterine environmental factor, and if this factor is amenable to intervention, improving the intrauterine environment may be used to improve dietary intake and reduce the risk of adverse consequences in later life.

Twin studies offer a unique opportunity to distinguish between environmental and genetic influences [15]. Differences within dizygotic twin pairs can be a function of both genetic and non-genetic factors, whereas differences within monozygotic pairs are nearly always caused by non-genetic factors [16]. If genetic factors do not play a major role in the association between birth weight and dietary intake, one would expect that *both* for dizygotic and for monozygotic twins, the twin with the lower birth weight from each pair will also have the unhealthiest dietary intake compared to the co-twin with the higher birth weight.

If, however, genetic factors do play a role, this association would hold true only for dizygotic twins, and not for monozygotic twins.

The aim of this twin study is to investigate whether lower birth weight is associated with dietary intake in later life, and whether, based on the comparison of the association in monozygotic and dizygotic pairs, the association is due to intrauterine environmental or genetic factors (Figure 1).

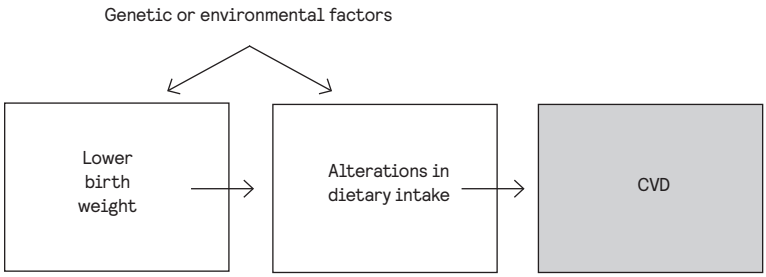

FIGURE 1
The postulated relations among birth weight, alterations in dietary intake and metabolic and cardiovascular disease. The aim of the study is to investigate whether the previously observed association between lower birth weight and alterations in dietary intake is influenced by genetic or environmental factors. CVD, cardiovascular disease

MATERIALS AND METHODS

PARTICIPANTS

Between 1985 and 1990, 160 adolescent (age 13 to 22 years) twin pairs and their parents took part in a study on cardiovascular risk factors [17-22]. All twins were still living were their parents. Details of the study have been described previously [19]. Parents of offspring underwent assessment for cardiovascular risk factors and responded to a large number of inventories. A survey on birth weight and gestational age was sent to the mothers a few weeks ahead of their visit to our department, allowing them to obtain these data from birth certificates. After visits to the department, including blood draws for zygosity assessment, data on dietary intake were collected in 120 twin pairs and their parents. The previously collected data were now analysed since it was only recently that Dutch hunger winter studies suggested an effect of the intrauterine environment on dietary intake in later life.

A flow chart of the study population selection and final study sample is presented in Figure 2. Data from opposite-sex dizygotic twin pairs (n=17) were excluded because of sex differences within a pair on birth weight. Data from eight twin pairs were not used because of missing information from one or both co-twins on either birth weight or dietary intake. Data from another 9 twin pairs were excluded from analysis because information written in the dietary records was too vague or unreadable to make a proper interpretation of foods actually

consumed. Thus, data of 39 dizygotic and 47 monozygotic twin pairs was available for analysis. The study was approved by an institutional review committee and all subjects gave informed consent.

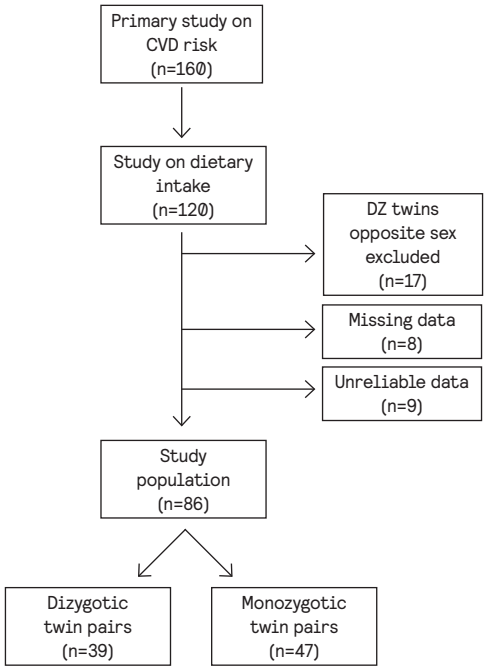

FIGURE 2
Flow chart of the study population. CVD, cardiovascular disease; DZ, dizygotic

MEASUREMENTS

Height and weight measurements and body mass index (BMI; in kg/m^2) calculations were done in a standardized way. Dietary intake was assessed using a two-day dietary record on one weekday and one weekend day. Dietary records and detailed written instructions were given to the participating families on the day of the study visit. In addition, oral instructions were given by trained dieticians. For the sake of clarification each dietary record contained an example of a completed record for one day. Parents were asked about preparation of dinner in a detailed manner. Within three weeks after returning the food records participants were contacted by telephone in case data were missing or unclear. Data were coded by two clinical dieticians who were not aware of the birth weight of the participants. Coding was done using a dietary analysis program based on the Dutch Food Composition Database (NEVO) [23]. Food products that were missing from this database were evaluated and matched to similar products in the database. Daily energy intake was expressed as kilocalories (kcal) and intakes of protein, carbohydrates, total fat and saturated fat were expressed as percentages of total energy intake (E%). Intake of dietary fibres was expressed as grams per 1000 kcal of total energy intake.

STATISTICAL METHODS

In the total group of twins linear regression analysis was used to examine the influence of birth weight on dietary intake after adjustment for age, sex and current weight [6, 8, 20]. This analysis was performed in Stata 13 including family ID as a cluster variable to account for non-independence of family members. An interaction analysis was performed to investigate whether sex, zygosity, current weight or current BMI influenced the associations between birth weight and dietary intake by introducing a product term of these variables and birth weight into the regression model. We compared twins with the lower birth weight from each pair with their co-twins with the higher birth weight [20, 21]. For this intra-pair analysis, a paired t-test was used [24]. To investigate the influence of intrauterine environmental or genetic factors, we compared the differences within twin pairs between dizygotic and monozygotic twin pairs, using independent samples t-tests.

As a first intra-pair analysis the comparison of dietary intake between twins with the lower and the higher birth weight is simple and illustrative. However, twin pairs that differ 1 gram in birth weight are not differentiated from twin pairs differing many hundreds of grams in birth weight. As a further analysis, linear regression analysis was used to analyse whether intra-pair differences in birth weight influenced intra-pair differences in dietary intake after adjustment for differences in current weight in dizygotic and monozygotic twins [21, 22]. An interaction analysis was performed to investigate whether sex, zygosity, gestational age, differences in current weight or differences in current BMI influenced the associations between intra-pair differences in birth weight and intra-pair differences in dietary intake.

To check the validity of reported energy intake across groups we calculated the ratio of energy intake to predicted basal metabolic rate of all individuals [25]. Predicted basal metabolic rate was calculated using the Schofield equations based on age, gender and weight [26]. A ratio of energy intake to basal metabolic rate lower than 1.34 was suggested to reflect underreporting [25]. There were no significant differences in underreporting between co-twins with lower birth weight and co-twins with the higher birth weight (P=0.24).

Results are expressed as mean (standard deviation) or regression coefficient (95% confidence intervals). A two-tailed P-value < 0.05 was considered to indicate statistical significance. IBM SPSS Statistics for Windows (version 20.0) was used for analysis of the data, except the first regression analysis in all twins, which was performed in Stata 13.

RESULTS

ASSOCIATION OF BIRTH WEIGHT WITH DIETARY INTAKE

In the total group of twins, birth weight was negatively associated with intake of saturated fat after adjustment for age, sex and current weight

(*P*=0.005; Table 1). Analyses without adjustment for current weight or after adjustment for current BMI instead of current weight, showed similar results (data not shown).

TABLE 1
Association between birth weight and macronutrient intake in the total group of twins (n=172)

	Beta (95% CI)	*P*
Energy (kcal)	-98 (-284.5 to 88.2)	0.3
Protein (E%)	-0.2 (-1.1 to 0.7)	0.6
Carbohydrates (E%)	1.3 (-0.5 to 3.2)	0.1
Total fat (E%)	-1.1 (-2.7 to 0.5)	0.2
Saturated fat (E%)	-1.2 (-2.1 to -0.4)	0.005
Fibres (g/1000 kcal)	0.2 (-0.7 to 1.2)	0.6

Data represent betas (95% confidence interval) per kg birth weight after adjustment for age, sex and current weight and including family ID as a cluster variable. E%, percentage of total energy intake

INTRA-PAIR DIFFERENCES

The differences in birth weight between the co-twins with the lower birth weight and those with the higher birth weight from each pair were similar for dizygotic and monozygotic twin pairs (363 g and 291 g, respectively; *P* for the difference, 0.2; Table 2). Co-twins with the lower birth weight were shorter in later life than their co-twins with the higher birth weight. Co-twins with the lower birth weight had a significantly lower body weight at adolescent age than their co-twins with the higher birth weight (*P*=0.03). BMI in later life did not differ between co-twins with the lower and co-twins with the higher birth weight.

In all twins, co-twins with the lower birth weight from each pair had a total energy intake that was 115 kcal higher than their co-twins with the higher birth weight (Figure 3A, left panel, *P*=0.04). To investigate whether this difference was influenced by intrauterine environmental and/or genetic factors, we compared dizygotic and monozygotic twin pairs. This difference in total energy intake was not different between dizygotic and monozygotic twin pairs (Figure 3A, right panel, 147 kcal vs. 88 kcal respectively, *P* for difference between dizygotic and monozygotic twin pairs, 0.6).

Furthermore, co-twins with the lower birth weight from each pair had an energy adjusted intake of saturated fat that was 0.7 E% higher compared to their co-twins with the higher birth weight (Figure 3B, left panel, *P*<0.05). This difference in intake of saturated fat was similar in dizygotic and monozygotic twin pairs (Figure 3B, right panel, 0.6 E% vs. 0.8 E% respectively, *P* for difference between dizygotic and monozygotic twin pairs, 0.8). No significant differences were found between co-twins with the lower and co-twins with the higher birth weight in intake of other macronutrients (Table 2).

TABLE 2
Clinical characteristics and intake of total energy and macronutrients in the co-twins with the lower and co-twins with the higher birth weight in all twin pairs and dizygotic and monozygotic twin pairs separately

	All Twin Pairs n=86			**Dizygotic Twin Pairs n=39**			**Monozygotic Twin Pairs n=47**		
Clinical characteristics	Co-twins with lower birth weight	Co-twins with higher birth weight	*P*	Co-twins with lower birth weight	Co-twins with higher birth weight	*P*	Co-twins with lower birth weight	Co-twins with higher birth weight	*P*
N (male)	86 (41)	86 (41)	-	39 (19)	39 (19)	-	47 (22)	47 (22)	-
Birth weight (g)	2311 ± 521	2635 ± 515	< 0.001	2325 ± 501	2688 ± 550	< 0.001	2300 ± 542	2591 ± 486	< 0.001
GA (weeks)	37.3 ± 2.8	37.3 ± 2.8	-	37.2 ± 2.7	37.2 ± 2.7	-	37.5 ± 2.9	37.5 ± 2.9	-
Age (years)	16.7 ± 2.0	16.7 ± 2.0	-	17.3 ± 1.9	17.3 ± 1.9	-	16.3 ± 2.0	16.3 ± 2.0	-
Current height (cm)	171.8 ± 8.7	173.2 ± 9.3	0.007	173.0 ± 7.3	175.3 ± 8.7	0.03	170.9 ± 9.7	171.5 ± 9.6	< 0.05
Current weight (kg)	58.8 ± 9.1	60.2 ± 8.7	0.03	60.6 ± 8.0	62.6 ± 8.4	0.1	57.3 ± 9.7	58.1 ± 8.4	0.2
BMI (kg/m^2)	19.9 ± 2.2	20.0 ± 2.1	0.4	20.2 ± 2.0	20.4 ± 2.0	0.6	19.6 ± 2.4	19.7 ± 2.1	0.4
Nutrient intake									
Energy (kcal)	2639 ± 703	2524 ± 743	0.04	2726 ± 714	2579 ± 639	0.1	2567 ± 693	2479 ± 824	0.2
Protein (E%)	15.0 ± 2.7	15.4 ± 3.2	0.2	14.7 ± 2.6	15.2 ± 2.8	0.3	15.2 ± 2.9	15.6 ± 3.4	0.4
Carbohydrates (E%)	49.1 ± 5.3	49.4 ± 5.6	0.5	49.4 ± 5.6	49.3 ± 6.5	1.0	48.8 ± 5.1	49.6 ± 4.9	0.3
Total fat (E%)	35.6 ± 5.0	34.8 ± 5.1	0.2	35.6 ± 5.3	35.0 ± 5.4	0.5	35.6 ± 4.8	34.6 ± 4.8	0.2
Saturated fat (E%)	14.8 ± 2.7	14.1 ± 3.0	< 0.05	14.6 ± 2.7	14.0 ± 2.8	0.2	15.0 ± 2.8	14.2 ± 3.2	0.1
Fibres (g/1000 kcal)	23.8 ± 8.5	24.4 ± 8.6	0.4	24.1 ± 9.7	25.3 ± 10.0	0.4	23.5 ± 7.6	23.6 ± 7.3	0.8

Data represent means (± SD). A paired t-test was used to calculate the differences between co-twins with the lower birth weight and co-twins with the higher birth weight.. E%, percentage of total energy intake; GA, gestational age

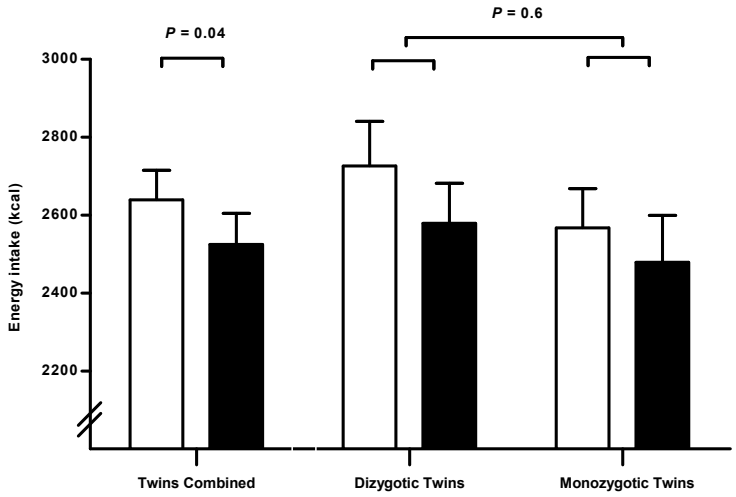

FIGURE 3A
Mean and SEM of total energy intake (kcal) in co-twins with the lower birth weight (white bars) and co-twins with the higher birth weight (black bars) from each pair in all twins and dizygotic and monozygotic twins separately. *P*-values are given for comparisons in intake within twin pairs as well as comparisons in differences between dizygotic and monozygotic twin pairs, and are calculated using the paired t-test.

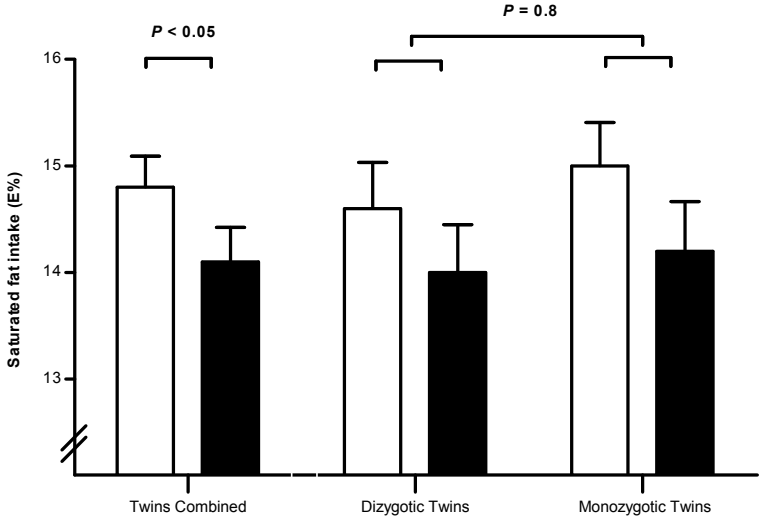

FIGURE 3B
Mean and SEM of saturated fat intake (E%) in co-twins with the lower birth weight (white bars) and co-twins with the higher birth weight (black bars) from each pair in all twins and dizygotic and monozygotic twins separately. *P*-values are given for comparisons in intake within twin pairs as well as comparisons in differences between dizygotic and monozygotic twin pairs, and are calculated using the paired t-test.

INTRA-PAIR ASSOCIATIONS

To further explore the relation between birth weight and dietary intake, we determined the associations between intra-pair differences in birth weight and intra-pair differences in dietary intake. Table 3 shows that intra-pair differences in birth weight tended to be negatively associated with intra-pair differences in total energy intake in all twin pairs, after adjustment for differences in current weight (*P*=0.07). The larger the difference in birth weight, the higher the total energy intake in the twin with the lower birth weight compared to the co-twin with the higher birth weight. To investigate whether this association was influenced by intrauterine environmental and/or genetic factors, we compared dizygotic and monozygotic twin pairs. This association was similar in dizygotic and monozygotic twin pairs (β: -238, [95% confidence interval: -662 to 185] kcal per kg birth weight vs. -265 [-643 to 113] kcal per kg birth weight respectively, *P* for the difference between dizygotic and monozygotic twins, 0.9; Table 3).

Furthermore, intra-pair differences in birth weight were negatively associated with intra-pair differences in intake of total fat and saturated fat in all twin pairs, after adjustment for differences in current weight (for total fat *P*=0.06; for saturated fat *P*=0.04). Again, these associations were similar in dizygotic and monozygotic twin pairs (for total fat β: -2.8 [-6.7 to 1.2] vs. -3.0 [-7.6 to 1.7] respectively, *P* for the difference, 0.9; for saturated fat β: -1.6 [-3.8 to 0.6] vs. -2.2 [-5.0 to 0.6] respectively, *P* for the difference, 0.9; Table 3).

Additionally, intra-pair differences in birth weight were positively associated with intra-pair differences in intake of dietary fibres (*P*= 0.04). The larger the difference in birth weight, the lower the intake of dietary fibres in the twin with the lower birth weight compared to the co-twin with the higher birth weight. Again, these associations were similar in dizygotic and monozygotic twin pairs (β: 2.0 [0.3 to 3.6] vs. 1.8 [-1.5 to 5.2] respectively, *P* for difference between dizygotic and monozygotic twin pairs, 0.9; Table 3).

Analyses without adjustment for differences in current weight or after adjustment for differences in BMI instead of differences in current weight, resulted in similar outcomes (data not shown).

INTERACTION ANALYSES

Interaction analysis indicated that the association between birth weight and dietary intake in the total group was not significantly modified by zygosity, gestational age, current weight or current BMI (data not shown). The association between birth weight and energy intake in the total group was stronger in boys (*P* for interaction <0.05). This effect modification by sex, however, was not found in the further intra-pair analyses of the association between birth weight and energy intake nor in the analyses of the association between birth weight and intake of other macronutrients (in the total group and intra-pair analyses). Further interaction analyses indicated that the association between

intra-pair differences in birth weight and differences in energy intake was weaker in twin pairs with larger differences in current weight (*P* for interaction <0.01), but effect modification by current weight was not found in the total group analyses nor in intra-pair analyses of the associations between differences in birth weight and differences in intake of other macronutrients. The associations between intra-pair differences in birth weight and intra-pair differences in dietary intake were not significantly influenced by zygosity or differences in BMI (data not shown).

TABLE 3
Association between intra-pair difference in birth weight and intra-pair difference in macronutrient intake in all twin pairs and dizygotic and monozygotic twin pairs separately

	All Twin Pairs n=86		**Dizygotic Twin Pairs n=39**		**Monozygotic Twin Pairs n=47**		***P* for difference between DZ and MZ**
	Beta (95% CI)	*P*	Beta (95% CI)	*P*	Beta (95% CI)	*P*	
Energy (kcal)	−249 (−522 to 25)	0.07	−238 (−662 to 185)	0.3	−265 (−643 to 113)	0.2	0.9
Protein (E%)	0.3 (−1.3 to 1.8)	0.7	−0.2 (−1.9 to 1.5)	0.8	0.9 (−1.7 to 3.6)	0.5	0.7
Carbohydrates (E%)	1.8 (−1.0 to 4.7)	0.2	1.9 (−2.8 to 6.5)	0.4	1.8 (−1.9 to 5.5)	0.3	0.9
Total fat (E%)	−2.8 (−5.8 to 0.1)	0.06	−2.8 (−6.7 to 1.2)	0.2	−3.0 (−7.6 to 1.7)	0.2	0.9
Saturated fat (E%)	−1.8 (−3.5 to −0.1)	0.04	−1.6 (−3.8 to 0.6)	0.1	−2.2 (−5.0 to 0.6)	0.1	0.9
Fibres (g/1000 kcal)	1.9 (0.1 to 3.7)	0.04	2.0 (0.3 to 3.6)	0.02	1.8 (−1.5 to 5.2)	0.3	0.9

Data represent betas (95% confidence interval) per kg birth weight after adjustment for differences in current weight. In the last column *P*-values are given for differences in intra-pair associations between DZ and MZ twin pairs, tested with interaction analysis using zygosity as interaction term. DZ, dizygotic; MZ, monozygotic: E%, percentage of total energy intake

DISCUSSION

In line with previous studies in singletons [5, 6, 8] we found in intra-pair analyses in an adolescent twin population that lower birth weight was related to higher total energy intake, higher intake of (saturated) fat and lower intake of dietary fibres. These intra-pair analyses in same sex twin pairs eliminate effects of multiple confounding factors such as sex, gestational age and maternal factors like smoking en social class. In addition, with intra-pair analyses in monozygotic twins also confounding by genetic factors is removed. The size and direction of the intra-pair differences and associations were similar in monozygotic and dizygotic twin pairs. This similarity in the intra-pair differences and intra-pair associations between monozygotic and dizygotic twin pairs suggests that the relation of birth weight with these alterations in dietary intake in later life is independent of genetic factors. These data are compatible with the hypothesis that the association between lower birth weight and alterations in dietary intake is due to intrauterine environmental factors.

Although studies in individuals that were exposed to famine in utero may have been influenced by selection [14], our findings are in line with

the results of two studies demonstrating that prenatal exposure to famine is associated with higher intake of total energy and fat in adulthood [10, 11]. More evidence for the importance of non-genetic factors comes from experimental studies in animals by showing that manipulation of the intrauterine environment can influence eating habits of the offspring [27-29]. Taken together, the results of these studies in combination with our twin study demonstrate that the origin of the association between birth weight and dietary intake lies in the intra uterine environment rather than in the genes of the foetus. These findings suggest that improving the intrauterine environment may positively influence dietary intake in later life.

The molecular mechanisms underlying this programming of appetite are not clear. Several studies have emphasised the important role of leptin in the programming of appetite. Intrauterine growth restricted offspring from undernourished rat dams developed hyperphagia, hyperleptinaemia and obesity in adult life [28], findings that are thought to be induced by peripheral and central leptin resistance [30, 31]. More recently, it has been suggested that the programming of appetite in rats may be reversible by the treatment of leptin injections in a late phase of developmental plasticity [32]. Another hypothesis is that maternal undernutrition leads to an altered set point of the hypothalamic-pituitary-adrenal (HPA) axis in the foetus which causes an increase in its circulating glucocorticoids [33]. As the administration of glucocorticoids in healthy men has shown to stimulate food intake [34], these higher levels in intrauterine growth restricted children could ultimately lead to altered dietary intake , as observed in our study. Unfortunately, in our study, leptin and cortisol levels are not available. Regardless the underlying pathophysiological route, evidence is growing for the involvement of epigenetics in the programming of metabolic disease, suggesting that alterations in dietary intake may be caused by epigenetic changes in the offspring DNA.

It could be proposed that the association between birth weight and dietary intake is due to differences in physical activity [10, 11]. However, epidemiological studies demonstrated that birth weight was not related to physical activity [35, 36] and adjustment for physical activity in a previous study did not influence the results on macronutrient intake [8]. Furthermore, the association between lower birth weight and altered dietary intake may be influenced by a higher basal metabolic rate in individuals born with a lower birth weight [37, 38]. Although we do not have data on basal metabolic rate in our sample of twins, we did perform our analyses with adjustments for age, current weight and/or BMI, factors that mostly determine basal metabolic rate.

Some potential limitations regarding the methodology of this study can be taken into consideration. Underreporting of unhealthy foods is a disadvantage in most methods of dietary intake assessment. We cannot exclude the possibility that underreporting influenced the results of our study. However, we expect that this underreporting would have

resulted in an underestimation of the true effect of birth weight on dietary intake. An advantage of dietary records in our study is that they do not depend on memory as compared to food frequency questionnaires and 24 hours recalls, and thus allow qualitative measurements of the amounts and types of foods at the time they are actually consumed.

It has been suggested that early life nutrition plays an important role in food preference and the development of obesity in later life [39, 40]. Similar to previous studies investigating the relation of birth weight with metabolic and cardiovascular risk [5-8], we did not use data on postnatal feeding. Considering the relevance of this issue, however, future research in this field should try to take into account the influence of early life nutrition on dietary intake in later life.

It could be argued that birth weight in twins are a poor model for differences in birth weight in singletons since intrauterine growth in twins is different from that in singletons [41]. However, the association between birth weight and saturated fat intake in the total group of our twin cohort was similar to the association in singletons in previous studies [6]. In addition, birth weight in twins has been associated with many variables that have been related to birth weight in singletons, such as blood pressure, atherogenic profile, sympathetic activity and type 2 diabetes [20-22, 42]. Although intrauterine growth in twins may be different from that in singletons, the associations between birth weight and cardiovascular risk factors in twins suggest that birth weight in twins is relevant for the development of cardiovascular disease, and that differences in birth weight in twins can be used as a model for differences in birth weight in singletons.

In our study, there was an interaction between birth weight and sex in the total group analysis, such that the association between birth weight and energy intake was stronger in men than in women. This interaction, however, was not present in the intra-pair analysis nor in all other (intra-pair) associations between birth weight and macronutrients. Previous studies did not find this interaction between birth weight and sex for energy intake. However, two singletons studies did show stronger effects of birth weight on fat intake in boys than in girls [5, 6].

The effects we found in this study may seem small and, similar to previous studies [7, 11], there were no differences in current BMI between subjects with lower and subjects with higher birth weight . However, results from animal and observational studies consistently show that even minor improvements in dietary habits reduces risk on cardiovascular disease [43, 44]. Replacement of 1 E% from saturated fatty acids with polyunsaturated fatty acids lowers LDL cholesterol and is likely to produce a reduction in CVD incidence of 2-3% [43]. Furthermore, dietary fibres carry out a protecting effect on CVD risk by enhancing signals of satiety through a bulking effect, thereby controlling total caloric energy intake. Consuming an additional 7 g/day of total fibres lowers the risk of CVD with 9% [44]. Thus, the alterations we observed in our study may have considerable health effects when persisted throughout life.

Therefore, various health organizations highlight the importance of a fibre-rich diet with a total energy content that does not exceed energy expenditure and a limited intake of saturated fatty acids, for instance through the replacement with polyunsaturated fatty acids [45-47].

In summary, we found a higher intake of total energy and saturated fat in the twins with the lower birth weight from each pair compared to their co-twins with the higher birth weight. Also, negative associations were found between intra-pair differences in birth weight and differences in intake of total fat and saturated fat. We found a positive association between intra-pair differences in birth weight and differences in intake of dietary fibres. These differences and associations were similar in dizygotic and monozygotic twins, suggesting that intrauterine rather than genetic factors are responsible for the association between birth weight and dietary intake in later life. Future studies are needed to investigate which specific intrauterine environmental factors are responsible for the association between lower birth weight and alterations in dietary intake. If these intrauterine environmental factors are amenable to intervention, future studies should explore whether improving the intrauterine environment may be used to improve dietary intake and reduce risk of adverse consequences in later life.

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